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Evidence for Circadian Influence on Human Slow Wave Sleep During Daytime Sleep Episodes

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ABSTRACT

The occurrence of slow wave sleep within spontaneously initiated daytime sleep episodes was studied to examine hypothesized associations with prior wakefulness and circadian factors. There was a strong relationship between measures of slow wave sleep and the proximity of sleep episodes to the maximum of body core temperature. Those sleep episodes that began within 4 hours of the maximum in body core temperature contained significantly more slow wave sleep than did all other daytime sleep periods, approximating proportions typical of nocturnal sleep. Multiple regression analysis revealed no relationship between measures of slow wave sleep and prior wakefulness. These findings are consistent with an hypothesized approximately-12-hour rhythm in the occurrence of slow wave sleep and they underscore the influence imposed on human sleep by the endogenous circadian timing system.

DESCRIPTORS: Circadian rhythms, Slow wave sleep, Prior wakefulness, Naps, Body core temperature.

Slow wave sleep (SWS) propensity has long been associated with the duration of prior wakefulness and of subsequent sleep. In an early study of the factors influencing SWS measures, Webb and Agnew (1971) concluded that the amount of Stage 4 sleep that occurred during the first 3 hours of a sleep episode was primarily determined by the duration of prior wakefulness. With increasing time asleep, the amount of Stage 4 sleep declined. More recently, it has been reported that prior wakefulness may account for up to 91% of the variance in SWS amounts recorded in subsequent sleep episodes, and that time asleep may account for up to 96% of the variance in the exponential decline of slow wave sleep across a sleep episode (Knowles, MacLean, Salem, Vetere, & Coulter, 1986). On the basis of such findings, the presence of slow wave sleep is typically postulated to reflect a sleep need, which is accumulated during wakefulness and which is reversed as a function of elapsed sleep time (Borbely, 1982; Daan, Beersma, & Borbely, 1984).

Despite the well-established association between SWS propensity and the duration of prior wakefulness, a possible circadian influence on this sleep state has not gone completely unnoticed. For example, in the Webb and Agnew (1971) study, a circadian effect was "suggested but not proven," leading the authors to conclude that the circadian influence on Stage 4 occurrence "does not seem to be a major one." Hume and Mills (1977) also reported findings that suggested a modest circadian influence on the occurrence of slow wave sleep, but again concluded that such an influence was not significant relative to that of prior wakefulness.

The finding that slow wave sleep reappears toward the end of extended sleep episodes (Gagnon & De Koninck, 1984; Gagnon, De Koninck, & Broughton, 1985; Webb, 1986) has been cited in support of the hypothesis that there exists an approximately-12-hour rhythm in SWS tendency (Broughton, 1975, 1985), or that a damped ultra-

With deep affection, this paper is dedicated to Dr. Wilse B. Webb on the occasion of his 69th birthday.

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dian rhythm, with a shorter frequency, is responsible for the occurrence of slow wave sleep (Lubin, Nute, Naitoh, & Martin, 1973). Clarification of factors influencing the occurrence of slow wave sleep is important for a complete understanding of the nature and function of this stage of sleep. The implication of circadian involvement in the regulation of slow wave sleep would clearly require adjustments in the current concept of a strict relationship between slow wave sleep and prior wakefulness.

In previous reports (Campbell & Zulley, 1985; Zulley & Campbell, 1985), we showed that in addition to the well-established tendency for sleep to occur around the minimum of body temperature (Czeisler, Weitzman, Moore-Ede, Zimmerman, & Knauer, 1980; Zulley, Wever, & Aschoff, 1981), there was a robust tendency for spontaneously sleeping subjects to obtain shorter sleep episodes during the subjective daytime (i.e., "naps"). These sleep periods did not occur randomly, but rather showed a tendency to cluster broadly around the maximum point in the circadian course of body core temperature. This phase position corresponds to a time approximately 12 hours after the midpoint of the preceding major night's sleep. If an approximately-12-hour rhythm of SWS propensity is hypothesized, this would be the phase position at which SWS amounts would be expected to reach a second peak. The broad distribution of sleep episodes around the temperature maximum, and the relatively wide range of waking intervals preceding such sleep periods, made these data particularly well-suited for assessing the differential influences of prior wakefulness and circadian factors on the appearance of slow wave sleep. In the present report, the occurrence of slow wave sleep within these daytime sleep episodes is examined.

Method

Nine healthy subjects (mean age = 25.2 years) lived separately in a "disentrained" environment for 72 hours following one night of adaptation sleep. The disentrained environment was identical to conditions used in standard circadian research (Wever, 1979), with the added feature that few behavioral alternatives were available to the subjects. They were prohibited from reading, writing, listening to music, strenuous exercise, etc. In addition, subjects were specifically requested to "unstructure" their days by eating and sleeping when inclined to do so. This is in contrast to the normal instructions to organize one's days around three meals taken in normal sequence and a single, major "night's" sleep. Thus, our subjects were more likely to respond to periods of physiological sleep tendency by actually initiating sleep episodes, rather than by choosing to overcome transient periods of drowsiness by engaging in alternative behaviors. This was reflected in the increased number of sleep episodes and in total time spent asleep during disentrainment. (For a complete description of the environment and of overall sleep/waking characteristics, see Campbell & Zulley, 1985.)

During the entire experimental period, EEG and body core temperature were continuously recorded. A telemetric recording device (Glonner Biomes 80) was employed which permitted subjects complete freedom of movement around the isolation apartment. Sleep EEG was scored in 30-s epochs following standard procedures (Rechtschaffen & Kales, 1968). Records were scored by two independent scorers. Interscorer reliability was 90%, based on random 2–3 hour segments of sleep episodes. Body temperature was recorded using a standard indwelling rectal thermistor. Temperature values were output to paper each minute and hourly averages were calculated.

A sleep episode was scored when sleep continued for at least 30 min. Two successive sleep episodes were scored when separated by at least 60 min of wakefulness. Applying these criteria, 26 sleep episodes were initiated and terminated between 0600 and 2000 hours, during the 72-hour study period (see Table 1 for the number of sleep episodes contributed by each subject). Eight daytime sleep episodes continued for less than 30 min (mean duration = 10.2 min). These brief sleep periods comprised less than .1% of total sleep time recorded during the experimental period. They were not considered in these analyses because they differed from other naps not only in duration but also in structure. None of these brief daytime sleep episodes contained slow wave sleep.

Results

Figure 1 shows the distribution of sleep periods ("naps") within the 24-hour day, in relation to major nocturnal sleep episodes and in reference to the average course of body core temperature recorded during the period of disentrainment. Naps differed from major nocturnal sleep episodes not only on the basis of time of day of occurrence, but also with respect to their average durations. Naps continued for an average of 105.8 min (SD = 55.8), whereas major nocturnal sleep continued for an average of 528.0 min (SD = 162.2).

The average percentage of slow wave sleep (SWS) in naps did not differ significantly from average proportions recorded during the major nocturnal sleep episodes (15.3% (16.2 min) versus 14.9% (78.7 min)). However, the variability of slow wave sleep within naps was about twice that of slow wave sleep within the major nocturnal sleep periods. When median values were considered, a large difference in SWS measures became evident. Median SWS% in major nocturnal sleep was 14.1%; in naps, the median was 4.9%. On average, the first

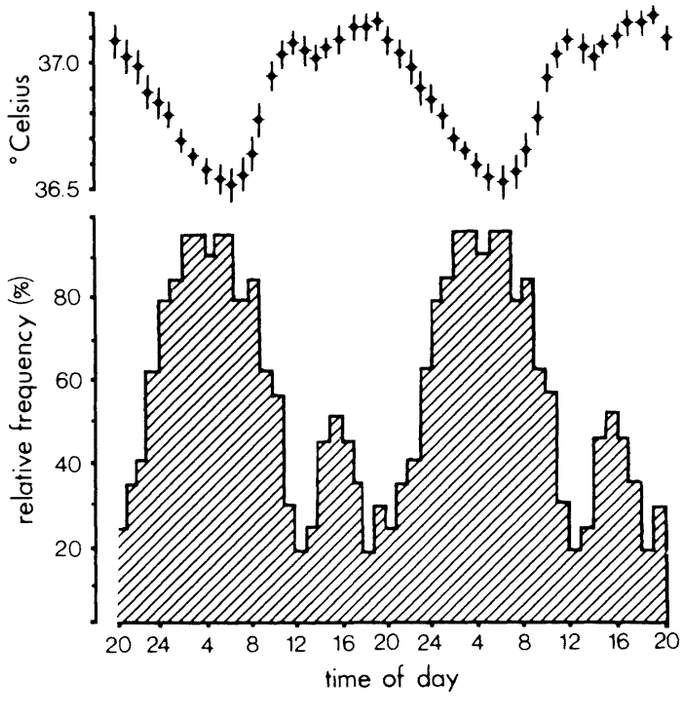

Figure 1. Distribution of sleep tendency as a function of time of day and relative to the average circadian course of body core temperature (±SEM) (double plotted). Temperature values are averaged across all subjects at hourly intervals. The histogram is based on all sleep recorded during the experimental period and shows the number of hours comprised totally or partially of sleep as a ratio of total hours available for sleep. The slight "dip" at the maximum of the averaged temperature curve probably reflects a masking effect of subjects initiating naps.

episode of slow wave sleep in a nap was initiated 13.9 hours (SD=2.4 hours) after the onset of slow wave sleep in the preceding nocturnal sleep episode.

Two general categories of naps could be identified within the nap distribution, based on their locations. Those naps in the middle of the distribution, with onset times between 1400 and 1700 hours (n=12), contained an average of 19.4% SWS (median=14.8%), compared to an average of 10.8% SWS (median=5.7%) for all other naps (n=14). Due to the substantial variability in proportions of slow wave sleep within the two categories of naps, this difference did not reach statistical significance. Nevertheless, a general tendency for naps with greater proportions of slow wave sleep to cluster around a particular time of day was apparent from this relatively gross classification of sleep episodes.

It was reasoned that a more accurate measure of relative circadian phase position of naps could be obtained by referencing each nap's onset to its respective temperature phase, rather than simply to time of day. Thus, the interval between each nap onset and the absolute maximum of body core temperature in the corresponding circadian day was calculated. Because of the extremely basal, static conditions of the disentrained environment, it seemed reasonable to assume that the maximum temperature values employed in this analysis accurately reflected the circadian course of body temperature, rather than simply reflecting "evoked effects" of exercise or transient increases in activity. However, least-squares cosine fits were also applied to the temperature curves, to provide an alternative reference point (i.e., acrophase) for calculations of the relative phase positions of naps. Cosine fits were carried out following calculation of the best fitting period (tau) for each circadian day. The difference, in hours, between nap onset and corresponding acrophase was then calculated.

The intervals between nap onsets and corresponding temperature maxima ranged from 1.5–11.5 hours (see Table 1). All but three of the naps occurred prior to the maximum temperature value. As shown in Figure 2a, there was a significant re-

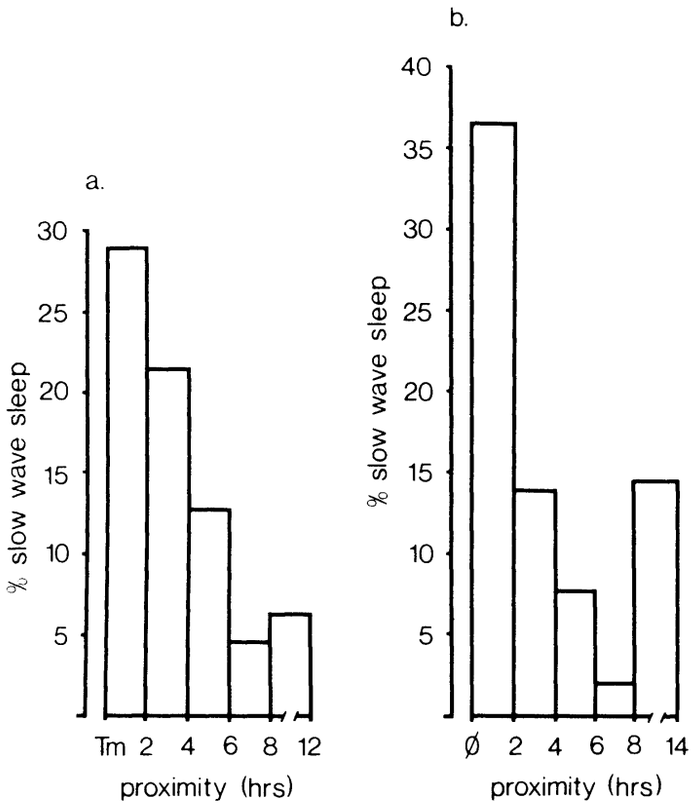

Figure 2. Average percentages of slow wave sleep (SWS) contained in naps as a function of their proximity to the respective circadian temperature maxima. In Figure 2a, proximity to absolute temperature maximum is shown. Mean and (median) SWS percents were as follows: within 2 hours: 28.4% (23.3%), 2–4 hours: 21.8% (16.7%), 4–6 hours: 12.7% (1.1%), 6–8 hours: 4.7% (4.1%), and 8–12 hours: 6.4% (6.6%) (this block comprises 4 hours, because only 4 naps fell within this range). In Figure 2b, proximity to acrophase is shown. Mean and (median) SWS percents were as follows: within 2 hours: 36.6% (37.6%), 2–4 hours: 13.9% (13.7%), 4–6 hours: 7.7% (3.2%), 6–8 hours: 2.1% (.7%), and 8–14 hours: 14.4% (this block comprises 6 hours, because only 2 naps fell within this range).

Table 1

Number of naps contributed by each subject, their onset times, proximity to temperature maximum (shown as the difference between onset time and corresponding absolute maximum or acrophase), length of preceding waking episode, and minutes and percentage of slow wave sleep in each nap

Subject I.D.	Number of Naps	Onset Time (hours)	Proximity to Temperature Maximum: Tmax Difference (hours)	Proximity to Temperature Maximum: Acrophase Difference (hours)	Prior Wakefulness (hours)	Slow Wave Sleep (min)	Slow Wave Sleep (%)
GLB	1	1330	8.5	7.1	2.4	11.5	5.1
	2	0633	8.5	13.8	1.3	15.5	8.2
	3	1215	9.8	8.6	2.4	18.5	16.3
ULB	1	1409	4.9	1.8	3.5	36.5	37.6
	2	1317	3.7	2.8	2.6	44.5	26.9
	3	1848	1.8	2.6	2.8	29.5	43.1
	4	1631	3.5	1.2	5.7	36.0	61.6
CWB	1	1240	7.3	7.5	2.3	0.5	0.7
	2	1631	3.5	3.6	2.6	22.0	17.5
	3	1556	3.0	1.6	5.2	8.0	11.1
	4	1452	7.9	6.6	6.1	0.0	0.0
	5	1750	5.2	3.6	2.5	0.5	1.1
WFB	1	1455	7.1	2.9	4.3	22.0	13.0
	2	1652	1.8	2.1	6.4	1.5	1.9
PZB	1	1412	1.7	1.1	5.2	19.0	23.3
	2	1027	3.5	6.6	1.5	8.5	4.7
JSB	1	1125	1.5	4.4	7.6	43.5	24.3
CBB	1	1441	1.3	0.5	4.3	19.0	49.4
	2	1542	3.3	2.3	5.2	13.5	16.7
	3	0933	11.5	3.7	1.4	0.0	0.0
	4	1701	3.9	3.7	4.7	22.0	14.3
RMB	1	1031	6.5	3.8	2.5	2.5	4.1
	2	0917	5.7	4.7	2.7	0.0	0.0
	3	0847	6.2	5.5	2.6	7.5	6.3
MHB	1	1414	7.7	6.4	1.9	0.0	0.0
	2	1528	7.5	4.4	6.5	0.0	0.0

lationship between the proximity of nap onsets to the temperature maximum (Tmax) and the percentage of slow wave sleep present in each nap. Naps initiated within 4 hours of Tmax (n=12) contained substantially greater proportions of slow wave sleep (mean=24.6%) than did all other naps (mean=6.8%) (Mann-Whitney $U=25$, $p<.002$, two-tailed test).

Similar results were obtained when naps were analyzed relative to their proximity to the corresponding acrophase (Figure 2b). Naps initiated within 4 hours of the acrophase (n=15) contained an average of over three times the proportion of slow wave sleep contained in all other naps (21.4% vs. 6.1%) (Mann-Whitney $U=38$, $p<.03$, two-tailed test).

The differential occurrence of slow wave sleep was not associated with differences in durations of the two categories of naps. The duration of naps initiated within 4 hours of Tmax, or within 4 hours of the acrophase (106.5 min and 96.9 min, respectively), was not significantly different from that of naps initiated greater than 4 hours from their corresponding temperature maximum (105.2 min and 118.0 min, respectively).

Multiple regression analysis was carried out on these data in an effort to determine the differential strengths of the relationships between prior wakefulness and SWS propensity and between proximity to the temperature maximum and SWS occurrence. (It is recognized that application of this statistical procedure to the current data set is problematic because intra- and intersubject variability are confounded. Individual data are provided in Table 1 to facilitate interpretation of the results of the analysis.)

The results of the multiple regression analysis are presented in Table 2. After partialling out the effect of prior wakefulness, the relationship between SWS measures and Tmax remained significant (for SWS%, $r=.51$, $p<.01$). Similarly, the relationship between SWS% and proximity of naps to the acrophase was significant ($r=.43$, $p<.03$), after partialling out prior wakefulness. In contrast, there was no relationship between prior wakefulness and SWS measures, after controlling for the effects of circadian phase. Thus, the significant predictor of SWS propensity within these daytime sleep episodes was the relative circadian phase at which they were initiated.

Table 2

Results of mutiple regression analysis: Partial correlation coefficients for the relationship between SWS measures and prior wakefulness (defined by the waking interval beginning with the offset of the preceding sleep episode) and the two measures of temperature maximum (absolute maximum and acrophase of the fitted cosine)

	Partial Correlation Coefficients (Multiple *R*'s in Parentheses)			
	Prior Wakefulness		Proximity to Temperature Phase	
Slow Wave Sleep Measures	Maximum	Acrophase	Maximum	Acrophase
Percent	−.023	.024	−.508** (.551)	−.431* (.485)
Minutes	−.003	.103	−.421* (.466)	−.205 (.297)

*$p<.03$, two-tailed, **$p<.01$, two-tailed.

Discussion

These findings show a strong relationship between the propensity for slow wave sleep and circadian factors (besides sleep itself), in the absence of the potentially confounding influences of prior wakefulness. As such, they provide considerable support for a postulated approximately-12-hour rhythm in SWS propensity (Broughton, 1975, 1985). Previous studies that have examined the structure of extended sleep have also suggested such a relationship, because there is a reappearance of slow wave sleep in the last hours of such sleep episodes (Gagnon & De Koninck, 1984; Gagnon et al., 1985; Webb, 1986).

However, interpretation of those results has been complicated by at least two methodological difficulties. First, no parameter, other than sleep itself, was recorded in the studies. Thus, there were no means by which to adequately measure the circadian phase of SWS occurrence. Secondly, with the exception of one study (Gagnon et al., 1985), an influence of prior wakefulness could not be ruled out, because a certain amount of intervening wakefulness is likely to occur within very long sleep episodes. For example, an average of over 40 min of wakefulness occurred within the last 3 hours of extended sleep periods in which the reappearance of significant amounts of slow wave sleep was reported (Gagnon & De Koninck, 1984). As such, this recurrence of slow wave sleep could be adequately explained in terms of the waking time within sleep. In the current study, an average of only 5.5 min of wakefulness occurred within naps. Moreover, waking time within naps was correlated with neither the percentage nor the absolute amount of subsequent slow wave sleep.

Why has the same strong relationship between slow wave sleep and circadian phase not been observed in major nocturnal sleep episodes? The scope of the present analyses was limited to daytime sleep episodes. One principal difference between typical nocturnal sleep episodes and the naps examined here, besides their circadian phase of occurrence, is the average duration of the waking intervals that precede them. The 26 naps analyzed here were preceded by an average of only 3.7 hours of wakefulness, whereas nocturnal sleep is commonly preceded by about 16 hours of wakefulness. It is well known that the relationship between prior wakefulness and slow wave sleep weakens substantially when waking intervals exceed about 30 hours (Webb & Agnew, 1971; Dinges, 1986). That is, there appears to be an upper threshold of waking, above which only modest increases in slow wave sleep are observed. One may hypothesize the existence of a corresponding *lower* threshold, below which SWS propensity is essentially unaffected by preceding wakefulness. Under conditions in which prior wakefulness falls below this threshold (e.g., spontaneous daytime sleep, extended sleep with brief intervening wakefulness), the influence of underlying circadian factors may become evident.

Conversely, under typical conditions of more extended waking durations, the influence of circadian factors may be dampened or completely masked by the influence of prior wakefulness. As noted earlier, such a dampened circadian influence on slow wave sleep has, indeed, been reported for major sleep episodes (Webb & Agnew, 1971; Hume & Mills, 1977). However, few studies have adequately examined the relationship between SWS tendency and waking intervals of relatively short duration, so the very existence, not to mention the limits, of this lower threshold of prior wakefulness must be considered speculative. Yet, limited data do suggest such a "floor effect" in the range of 3–6 hours (Bunnell, Bevier, & Horvath 1984; Campbell, 1987).

In summary, the sleep episodes considered in the present study may be viewed as reflecting the effects of a circadian influence on slow wave sleep, under conditions in which the influence of prior

wakefulness was minimized. SWS propensity was strongly associated with the phase of the endogenous circadian system at which sleep was initiated. This was the case regardless of the method used to identify the "maximum." Naps initiated within 4 hours of Tmax, or within 4 hours of acrophase, had over triple the amount of slow wave sleep per hour (14.7 and 12.7 min/hour, respectively) that was observed in naps initiated outside that range (4.1 and 3.7 min/hour). Though there are difficulties in the application of multiple regression analysis to these data (i.e., intra- and intersubject variability are confounded), the findings of such analyses do lend added support to the clear finding of a robust relationship between SWS occurrence and body core temperature (Figure 2).

Such an association between circadian phase and various other components of the sleep process is well established. Components of the REM sleep system, such as latency to, and duration of, the first REM episode are determined by the circadian phase of occurrence (Czeisler et al., 1980; Zulley, 1980). The duration and timing of major sleep episodes (Czeisler et al., 1980; Zulley et al., 1981), as well as those of sleep in the subjective daytime (Campbell & Zulley, 1985; Zulley & Campbell, 1985), are also under circadian control. The present findings underscore, and add a further dimension to, the extent of the intimate relationship between the endogenous circadian timing system and human sleep/wake organization. In so doing, they complicate the presumed relationship between the buildup of SWS propensity and prior time awake and suggest the need for a circadian component in the characterization of this process of sleep regulation.

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