Sleep and Activity Rhythms are Related to Circadian Phase in the Blind

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Study objectives: Sleep is controlled by both circadian and homeostatic mechanisms. As the light-dark cycle is the most important time cue in humans, blind individuals may have circadian rhythm disorders including sleep. The aim of the study was to assess sleep with simultaneous measurement of an endogenous marker of the circadian clock, namely 6-sulphatoxymelatonin (aMT6s).
Setting and participants: 59 registered blind subjects were studied in their own homes.
Design: Subjects completed daily sleep and nap diaries for at least four weeks, wore activity monitors continuously, and collected urine samples over 48 hours each week for 3-5 weeks for assessment of aMT6s rhythms.
Results: The most sensitive indicator of a circadian rhythm disorder was day-time napping. Subjects with normally entrained (NE) aMT6s rhythms had fewer naps of a shorter duration than abnormally entrained (AE) or free-running (FR) subjects. The timing of these naps was not random; significantly more naps occurred within a five-hour range before and after the aMT6s acrophase (phi (φ)) than outside this range. Disorders in the timing and duration of night sleep in AE subjects manifested as either a permanent advance (advanced sleep phase syndrome, ASPS) or delay (delayed sleep phase syndrome, DSPS). In FR subjects there were transient advances and delays in sleep timing that paralleled aMT6s timing with increased night sleep duration and reduced number and duration of day-time naps associated with a normal aMT6s phase.
Conclusions: Changes in sleep and activity rhythms reflect changes in circadian phase.
Key words: Blindness; sleep; napping; melatonin; circadian; activity; sleep disorder; advanced sleep phase syndrome (ASPS); delayed sleep phase syndrome (DSPS); free-running; non-24 hour sleep-wake syndrome

INTRODUCTION

IT IS WELL ESTABLISHED THAT SLEEP IS CONTROLLED by both homeostatic and circadian mechanisms.[1-6] Many sleep parameters, including sleep initiation, consolidation, structure, and EEG, have been shown to have a circadian component revealed primarily in "forced desychrony" experiments (review, 6). In such studies, subjects are forced to sleep for one-third of a "daily" cycle that is either longer or shorter than 24h. Sleep is thus attempted at all circadian phases, but out of synchrony with the 24h day. An alternative approach is to have subjects live on a very short day (e.g., 20, 90, 180 or 240 minutes), sleeping for one third of the "day" over a period of at least 24h, again forcing subjects to attempt to sleep at all circadian phases (review, 6). These highly complex experiments "demask" circadian rhythms by removing the effects of light and other external influences for extended periods.

Blind individuals, especially those with no light perception, may not be entrained by light and may therefore exhibit circadian rhythm disorders.[7-13] The types of circadian rhythms found in the blind have been classified as: 1) normally entrained to 24h; 2) abnormally entrained to 24h (phase delayed or phase advanced); 3) free-running at a period different from (usually greater than) 24h; and 4) unclassified with no discernible rhythm.[8,10-13] If a circadian rhythm disorder is present in blind subjects, it would be expected that sleep, partially under circadian control, would also be disrupted. Several epidemiological surveys have confirmed that the blind population has a higher incidence and severity of sleep disorder[14-19] than sighted individuals[20,21] although not all of these disorders can be attributed to a lack of light perception.[18] Several studies have also revealed the presence of a free-running sleep-wake rhythm in blind individuals, in both laboratory[9,22] and field conditions[10,11,22,23] and prior to melatonin administration studies.[24-26] Overall, however, the number of blind subjects studied has been small and any effect of abnormal circadian phase on sleep has been inconclusive.[10]

This paper describes the long-term assessment of the sleep-wake and activity rhythms under field conditions of 59 blind individuals with simultaneous assessment of an

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endogenous marker of the circadian clock, namely 6-sulphatoxymelatonin (aMT6s). The relationship between sleep and activity rhythms and the phase of the circadian clock has been assessed.

METHODS

Subjects

Fifty-nine registered blind people (17 female, 42 male; 29 with light perception or better [LP], 30 with no conscious light perception [NPL]; age range 19-72 years) were recruited from a database compiled to assess the incidence of sleep disorders in the blind.[16] Ethical permission for the study was granted by the University of Surrey Advisory Committee on Ethics and the Moorfields Eye Hospital Ethics Committee. Subjects were excluded if they were taking medications known to affect sleep and/or melatonin production (tricyclic antidepressants, monoamine oxidase inhibitors, serotonin reuptake inhibitors, benzodiazepines, neuroleptics, β-blockers, or sleeping medication). Informed consent was obtained from all subjects and included consent for the assessment of urine for a number of drugs (opiates, amphetamine, barbiturates, benzodiazepine, cocaine, cannabis, tricyclic antidepressants). Prior to the study, subjects underwent a full ophthalmological examination and interview and completed the Pittsburgh Sleep Quality Index.[27] The subject population suffered from a range of diseases and their duration and rapidity of blindness varied. The majority of subjects (80%) complained of a sleep disorder as assessed by the PSQI (score ≥5; 23/29 LP and 24/30 NPL subjects).

Study Schedule

Subjects completed daily sleep and nap diaries for at least four weeks, recording subjective sleep onset, offset, latency, duration, number and duration of night awakenings, sleep quality (9-point scale; 1=best sleep ever, 9= worst sleep ever) and the number and duration of naps. Naps were defined as any sleeps that occurred outside the bedtime period. Most of the subjects (49/59) also wore activity monitors (Motionloggers and Minimotionloggers, Ambulatory Monitoring Inc., New York, USA) continuously for the whole study. Activity data were subjected to cosinor analysis (Action3 software, Ambulatory Monitoring Inc.) to reveal the acrophase (phi (φ)), amplitude and mesor of the activity rhythm.

For 24 or 48 hours each week, subjects collected sequential four-hourly urine samples (8h overnight) for analysis of aMT6s, the major urinary metabolite of melatonin. Full details of the methods used to determine circadian rhythm type from the aMT6s rhythms are described in Lockley et al.[12]

Sleep and activity rhythms

To determine changes in sleep timing, regression lines were fitted through both the subjective onset and offset times for each individual. A rhythm was considered to be freerunning when the 95% confidence limits of the regression line did not cross 0 (i.e., 24 h [tau = 24 h + slope]). The same analysis was also performed on the midpoint time of subjective naps and the daily activity acrophase times.

Spectral analysis of activity data was performed (Action3 software) to reveal any multiple periodicities in the activity rhythms.

Sleep and activity in relation to circadian phase

In subjects that did not show freerunning aMT6s rhythms, the mean aMT6s acrophase time (phi (φ)) was used to define circadian phase. Multiple regression analysis was performed between the mean aMT6s acrophase, mean subjective sleep parameters, activity acrophase time, and age of the subject. In subjects with freerunning aMT6s rhythms, the regression line fitted through the aMT6s acrophase times was used to calculate the daily aMT6s acrophase for each person. Mean subjective sleep parameters were compared during a subjects' normal (aMT6s acrophase 24.00-06.00 h) and abnormal (aMT6s acrophase 06.00-24.00 h) circadian phase. For those subjects that passed through a full circadian cycle during the study, sleep, nap, and activity data were firstly expressed in relation to each individual's overall mean for each parameter and then grouped as a function of hourly aMT6s acrophase times. One-way ANOVA was used to calculate whether there was an overall significant change in these parameters with circadian phase (aMT6s acrophase). In all entrained and freerunning subjects, naps were assigned to groups within and outside a five-hour range around the daily aMT6s acrophase time.

RESULTS

aMT6s rhythms

The aMT6s rhythms in 49 of these subjects have been previously published in detail.[12] Using the aMT6s acrophase time, calculated by cosinor analysis, all the subjects (n=59) were classified into one of four categories; normally entrained to 24h (NE; phi range = 02.13 — 06.65 h, n = 30); abnormally entrained to 24 h (AE advanced; phi range = 20.30-01.00h, n=4 and AE delayed; phi range 07.20 - 14.25 h, n =5); freerunning (FR; tau range = 24.13 -24.79 h, n=17) and unclassified (UN; no discernible rhythm, n=3). One of the subjects clearly had a freerunning aMT6s rhythm but, due to lack of urine samples, an estimation of tau was not possible and this subject was excluded from analysis that required a tau estimation. Unclassified subjects were omitted from any further analy-

sis involving aMT6s rhythms.

Sleep and activity rhythms

Figure 1 shows the incidence of free-running behavioral rhythms (sleep, naps, activity) as assessed by regression analysis in subjects with free-running aMT6s rhythms. In all cases, the period of the behavioral rhythms was shorter than the corresponding aMT6s tau. Free-running behavioral rhythms were more likely to occur in those FR subjects with long aMT6s taus (7/8, 88%, aMT6s tau >24.5h), than those with shorter taus (3/8, 38%, aMT6s tau < 24.5 h) (Fig. 1). Some subjects (n=10) had FR behavioural rhythms but not FR aMT6s rhythms. In individuals with FR aMT6s rhythms, the incidence of a least one FR behavioral parameter (from sleep onset, sleep offset, naps, or activity acrophase) was higher (10/17, 59%) and its tau longer (p= 0.07, ANOVA; mean tau (± SD) = 24.12 ± 0.06 h) than those that did not have FR aMT6s rhythms (incidence 10/42, 24%; mean tau (±SD) = 23.98 ± .20h).

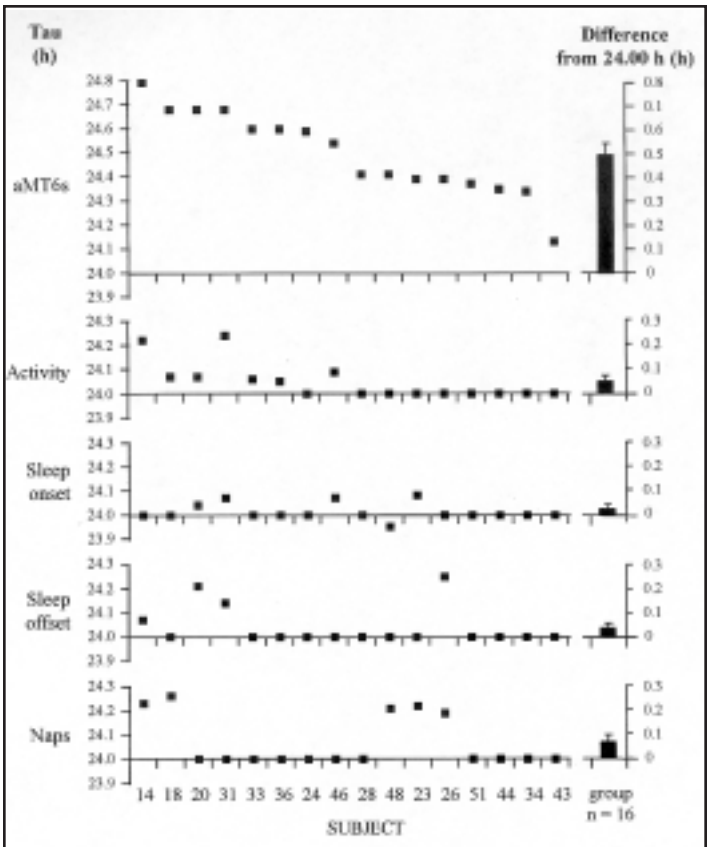

Figure 1. —Incidence of free-running behavioral rhythms in blind subjects with free-running aMT6s rhythms.

The figure shows the periodicity of aMT6s, activity, sleep and nap rhythms in 16 free-running NPL subjects (one FR is not shown — see text for details). The period (tau) is shown on the left vertical axis and subject numbers are shown on the horizontal axis. For the sleep, nap, and activity rhythms, all taus that were not significantly different from 24.00h have been plotted as 24.0h. The right vertical axis shows the overall mean (± sem) difference in the rhythms from 24.00 (group, n=16).

Naps as a marker of circadian rhythm abnormality

Figure 2 shows the relationship between subjective naps and aMT6s rhythm abnormality. There were significantly fewer naps of a shorter duration in subjects with normally entrained aMT6s rhythms (NE; n=30) compared to those with abnormally entrained (AE; n=9) and free-running (FR; n=17) aMT6s rhythms (p<0.05, ANOVA) (Fig. 2A

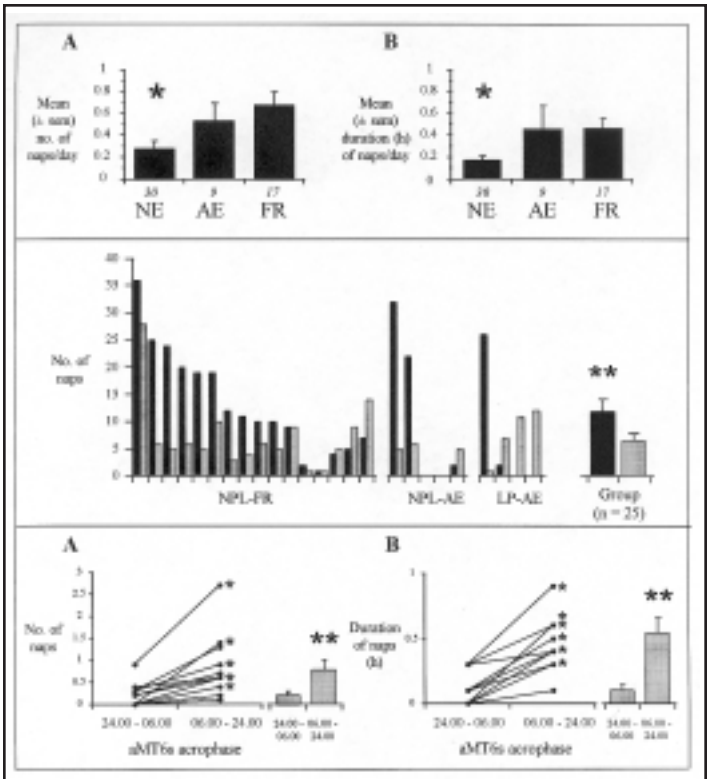

Figure 2. —Naps as a marker of circadian rhythmicity.

The upper panel shows the number (A) and duration (B) of self-rated naps in blind subjects with normally entrained (NE), abnormally entrained (AE), or free-running (FR) 6-sulphatoxymelatonin (aMT6s) rhythms. There were significantly fewer naps of a shorter duration in subjects with NE aMT6s rhythms (* p<0.05, ANOVA, Duncan's New Multiple Range), compared with the other subgroups. The numbers in italics represent the number of subjects per subgroup.

The middle panel shows the total number of self-rated naps within and outside a 5-h period before and after the calculated aMT6s acrophase for all subjects with abnormal aMT6s rhythms (free-running and abnormally entrained (NPL and LP)) both individually and grouped (mean ± sem, n=25). The vertical axis shows the total number of naps for the whole study. The black columns represent naps within the time range and the grey columns represent the naps outside the range. There were significantly more naps within the 5-h range before and after the aMT6s acrophase than at any other time (** p< 0.05, n=25, paired Student's t–test).

The lower panel shows the mean number (A) and duration (B) of self-rated naps per day in 11 individuals with freerunning aMT6s rhythms that passed, at least partially, through a normal (aMT6s acrophase 24.00 - 06.00h) and an abnormal (aMT6s acrophase 06.00 - 24.00h) phase. Most individuals had significantly more naps of a longer duration during the abnormal phase (06.00 - 24.00h) (*, p < 0.05, Student's t–test). The group mean (±sem) shown by the grey bars, also showed a significant increase in the number and duration of naps during the abnormal phase (**, p<0.05, paired Student's t–test).

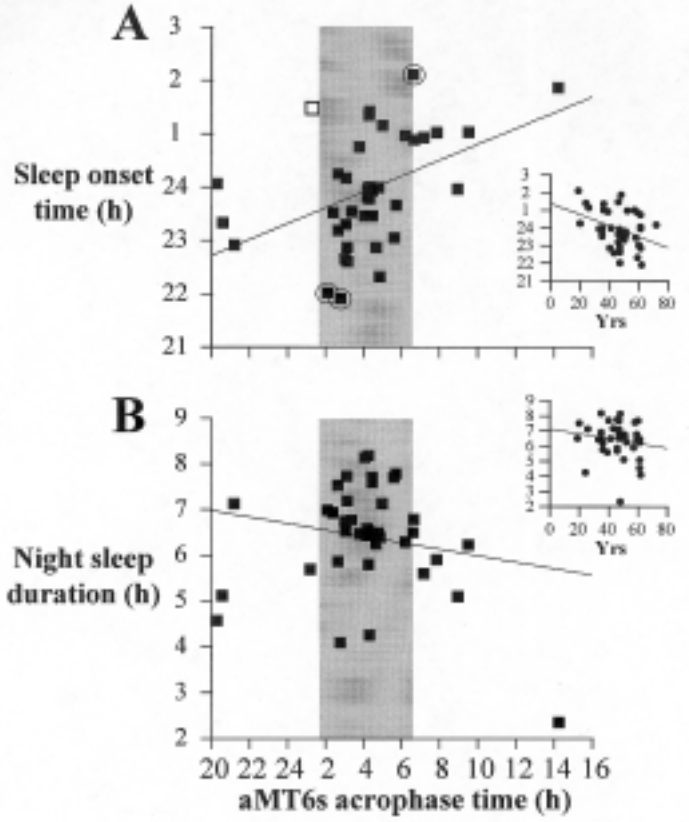

Figure 3.—Relationship between aMT6s acrophase time and sleep in entrained subjects.

The figure shows the relationship between mean subjective sleep onset (A), night sleep duration (B) and mean aMT6s acrophase time in normally and abnormally entrained subjects (n=39). The grey bars represent the mean aMT6s acrophase time ±2 SD for the NE subjects (n=30). Circled symbols show subjects with aMT6s acrophases within the normal range but exhibiting sleep phase disorder and the open square shows a subject with an advanced aMT6s phase but relatively delayed sleep onset (see text for details). The insets show the correlation between sleep onset and sleep duration with age. There is a significant positive correlation between sleep onset and aMT6s acrophase time after taking age into account (p<0.05, MANOVA). Conversely, there is a significant negative correlation between night sleep duration and aMT6s phase after taking into account any age effects (p<0.05, MANOVA).

and B upper panel). There were five individuals that did not nap at all during the study but they reportedly made a conscious effort not to do so.

In those subjects with FR and AE rhythms (n=25), there were significantly more naps (65%) within a 5-h range before and after the aMT6s phi (p<0.05, paired Student's t–test) compared to outside this range (Fig. 2 middle panel). In a few subjects, notably the LP subjects with AE rhythms, this was not the case. Of those FR subjects that passed through a normal (aMT6s phi, 24.00-06.00h) and abnormal (aMT6s phi, 06.00-24.00h) circadian phase during the study (n=11), there were significantly more naps of a longer duration when the aMT6s rhythm was abnormally timed (p<0.05, unpaired Student's t–test) (Fig. 2A and 2B lower panel).

Sleep, activity, and circadian phase relationships

Entrained subjects.

Thirty-nine subjects had aMT6s rhythms stably entrained to 24h (n=30 NE, n=9 AE). When controlled for age, sleep onset time and night sleep duration showed a significant relationship with aMT6s phase. Figure 3 shows the relationship between sleep onset and duration with aMT6s acrophase and age. When the aMT6s rhythm was advanced, sleep onset was advanced and night sleep duration was longest. When the aMT6s rhythm was delayed, sleep onset was delayed and night sleep duration was reduced (Fig. 3A and 3B). No other sleep parameters or activity showed a significant relationship with aMT6s phase when age effects were taken into account. The relationship between sleep onset time and aMT6s phase (Fig. 3A) allows the classification of these abnormally entrained subjects into those with advanced sleep phase syndrome (intrinsic type) (ASPS; n=3) and delayed sleep phase syndrome (intrinsic type) (DSPS; n=5) [28]. The subjects' stable but advanced or delayed sleep periods were associated with stable advanced or delayed aMT6s phase, respectively. There was one notable exception who had an advanced aMT6s acrophase time but a relatively delayed mean sleep onset (Fig. 3A, open square).

Figure 3A also shows that there were several subjects (n =3) whose aMT6s rhythms fell into the normal range (grey bars; mean ± 2SD; 1.7 - 6.6 h, n=30) but who appeared to have advanced (n=2) and delayed sleep (n=1) onset times (Fig. 3A, circled symbols). These abnormal sleep patterns are most likely due to their circadian phase position (Fig. 3A) as they have aMT6s acrophase times close to the limits of the normal range. In addition there was one LP subject who did not have rhythmic aMT6s production (classified as UN) but whose sleep was clearly phase delayed (Fig. 4F). Figure 4 shows examples of the different sleep disorders observed and the associated aMT6s rhythms ASPS (Figs. 4A-C), DSPS (Figs. 4D-F), and non-24 hour sleep-wake syndrome or free-running disorder (Figs. 4G-4I).

Free-running subjects.

Six subjects had aMT6s rhythms which passed through most (>75%) of a full circadian phase during the study. Figures 5 and 6 show the grouped analysis of sleep and activity data, plotted in relation to circadian phase as assessed by aMT6s acrophase time. Figures 5A and 5B show the change in the timing of sleep onset and offset in relation to aMT6s phase. There was anon-significant change (p=0.07) in sleep onset and a significant change in sleep offset (p<0.05) with aMT6s acrophase, with both parameters being relatively advanced when the aMT6s rhythm was advanced and relatively delayed when the

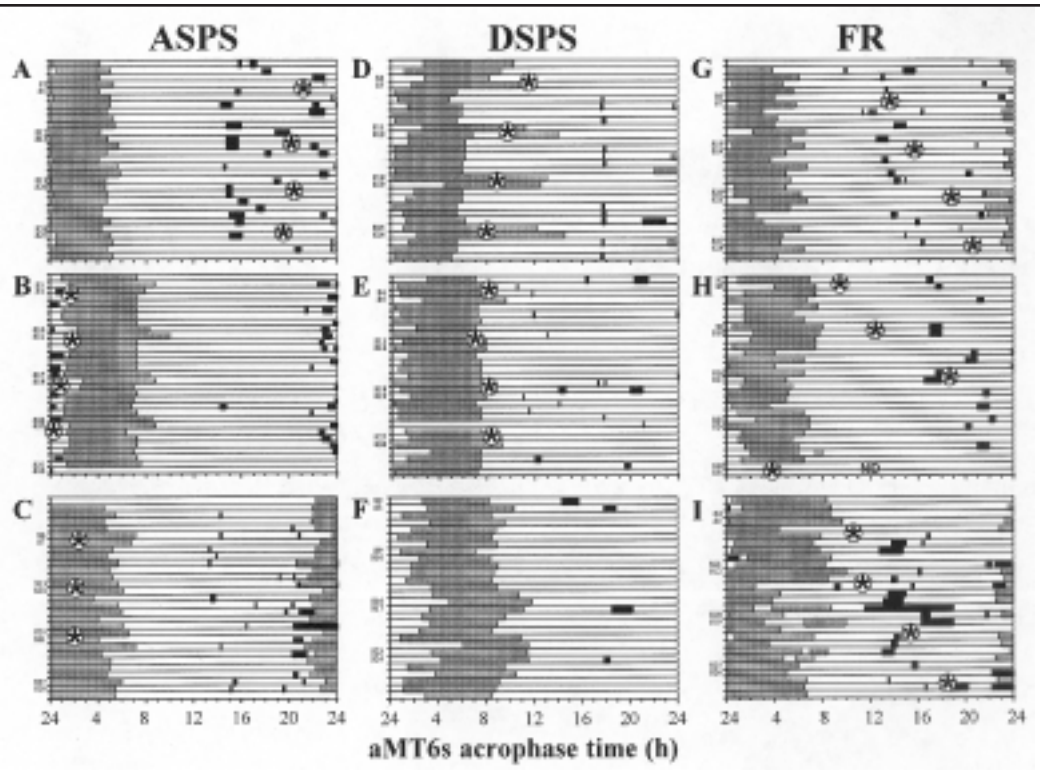

Figure 4. —Sleep and aMT6s disorders in blind subjects.

The figure shows subjective sleep and nap data and aMT6s acrophase times in subjects with advanced sleep phase syndrome (ASPS), delayed sleep phase syndrome (DSPS) and non-24 hour or free-running (FR) sleep-wake disorder. Sequential study days are on the vertical axis of each graph with weekends represented by "SS". Subjective sleep onset and offset times are shown by the grey bars and self-rated naps are represented by black bars. Circled asterisks show the aMT6s acrophase time for each 48h urine sampling period. See text for details of sleep classification.

aMT6s rhythm was delayed compared to the normal range (Fig. 5, grey bars). The duration of night sleep and day-time naps also changed significantly in relation to changes in aMT6s phase ($p<0.05$, Figs. 5C and 5D, respectively). Night sleep duration was minimal when the aMT6s rhythm was out of phase and greatest when the aMT6s rhythm was in a normal phase position (Fig. 5C). The number (data not shown) and duration of day-time naps (Fig. 5D) were maximal when the aMT6s rhythm was maximally out of phase and minimal when aMT6s was in a normal phase position.

The timing of the activity rhythm also changed significantly ($p<0.05$) in relation to aMT6s phase (Fig. 5E) in a similar manner to the timing of sleep (Figs. 5A and 5B). The activity acrophase was relatively advanced when the aMT6s was advanced and delayed when the aMT6s rhythm was delayed compared to a normal phase position (Fig. 5E).

Figure 6 shows the sleep parameters that did not change significantly with circadian phase. Sleep latency was longest when the aMT6s rhythm was phase delayed (Fig. 6A) but did not show an overall significant change. Similarly, the number and duration of night awakenings (Figs. 6B and 6C, respectively), total sleep duration (night time sleep duration + next day nap duration) (Fig. 6D), and subjective sleep quality (Fig. 6E) did not show any significant change with phase.

Spectral analysis of activity

Spectral analysis of the activity rhythms of 49 subjects revealed a significant relationship between the number of spectral peaks and aMT6s rhythm type. The majority of NE subjects (15/21, 71%) had only one spectral activity peak (tau ca. 24.00h) whereas the incidence of more than one spectral peak (tau ca. 24.00h and 12.00h) was significantly higher in subjects with abnormal aMT6s rhythms (AE, 78%, n=9; FR, 71%, n=17; $p<0.05$, χ^2-test).

DISCUSSION

This is the largest study to date which describes the simultaneous assessment of sleep, activity, and circadian phase in blind subjects. It confirms the deleterious association between an abnormally entrained or free-running circadian system and sleep and activity in blind subjects in the field.

Although most subjects (80%) had a sleep disorder according to the PSQI, not all of these sleep disorders were attributable to a disordered circadian system, as measured by aMT6s rhythms. Notwithstanding that sleep disturbances are multifactorial in origin, in general blind subjects with abnormal (AE, FR) aMT6s rhythms are more likely to have a circadian sleep-wake disorder (ASPS, DSPS, non-24h sleep-wake disorder) compared to those with normal

aMT6s rhythms.

In subjects with free-running aMT6s rhythms, given the strong social and environmental zeitgebers other than light associated with conventional living (e.g., work, meals, travel, activity, social interaction, scheduled sleep-wake periods), it is surprising that a number of subjects with FR aMT6s rhythms also demonstrated free-running behavioral rhythms (10/17; 59%). There were more FR rhythms in activity than in the other behavioral parameters. In addition, spectral analysis of activity also distinguished between those individuals with and without an abnormal aMT6s rhythm. The fact that activity assessment using actigraphs provides a large continuous data set may facilitate the ability to measure changes in the rhythm.

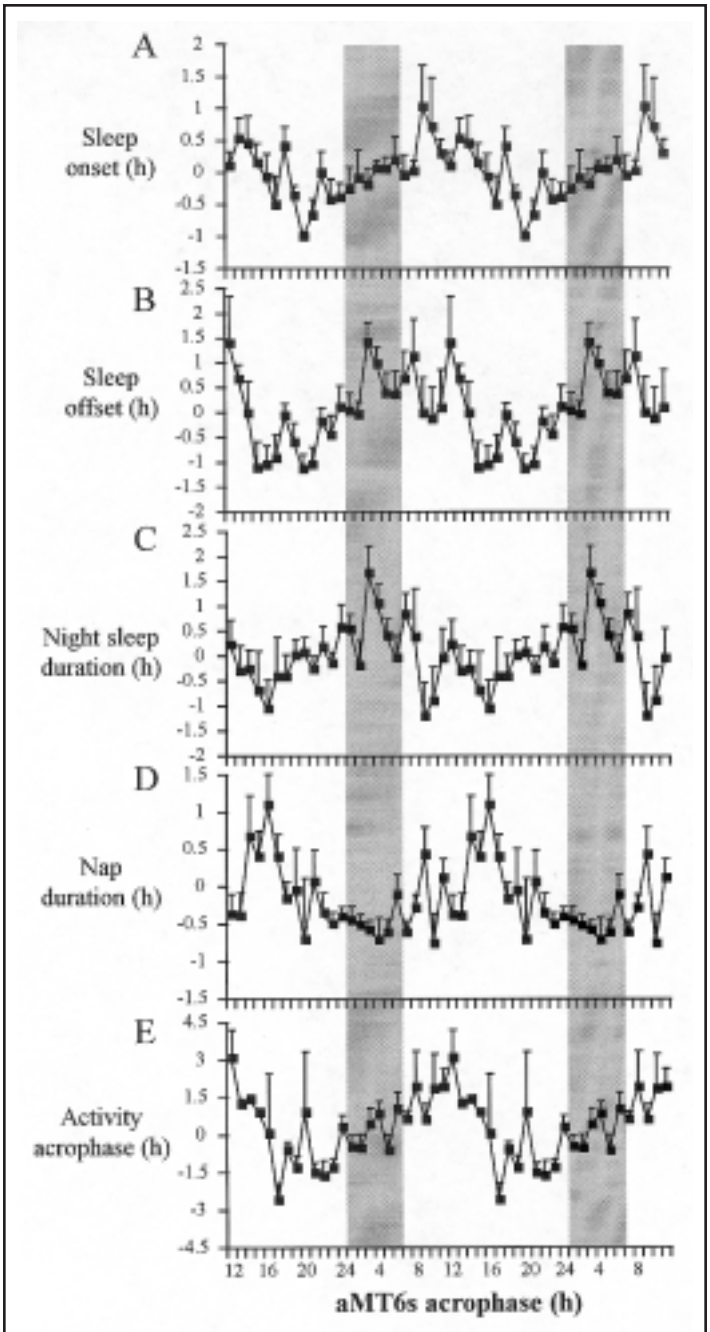

Figure 5. —Relationship between aMT6s phase and sleep and activity in free-running subjects.

The figure shows the mean (± sem) sleep parameters for six subjects and activity acrophase times for four subjects (with respect to each subjects' own mean) double-plotted against hourly aMT6s acrophase times. The grey areas represent the mean (± 2 SD) aMT6s acrophase time for normally entrained subjects (n=80, English and Arendt, unpublished results). For sleep onset, offset and activity acrophase positive values represent a relative advance compared to the mean whereas negative values represent a relative delay. All the parameters showed overall significant differences with respect to aMT6s phase ($p<0.05$, one-way ANOVA) except sleep onset ($p=0.07$). The number of naps also changed significantly (not shown) and paralleled the changes in nap duration.

It is clear from this study and our preliminary analysis[11] that the most reliable behavioral indicator of circadian rhythm abnormality was the incidence and duration of self-rated naps. The pattern of napping is observed as a cluster of naps occurring around the peak time of aMT6s. This pattern persists in abnormally entrained subjects and changes in parallel with changes in free-running aMT6s rhythms. In the FR subjects, the incidence and duration of naps dramatically increased when the aMT6s rhythm was in an abnormal phase position. It is likely that during this desychronized phase the observed nap pattern represents the endogenous circadian pressure (Process C) to sleep.[29,30] On the other hand, it could be argued that the napping merely reflects Process S (i.e., homeostatic compensation for night sleep deprivation) and of course this may influence the likelihood of naps. However, it is unlikely that compensatory naps would follow the circadian phase (Process C) as closely as we have demonstrated. The hypothesis that these naps reflect primarily a circadian mechanism is also supported by evidence of an association between sleep propensity and circadian phase.[5,6,9,31] As sleep and melatonin are probably ultimately driven by the same oscillator,[32] it is not surprising that they run in parallel in a free-running system. There is also the possibility that the daytime rise in melatonin plays a role in the timing and occurrence of naps; however, no experiment has yet been performed to show that this correlation is causative.

In this study, we have recorded the first detailed examples of advanced sleep phase syndrome (ASPS) and delayed sleep phase syndrome (DSPS)[28] in the blind, which have been confirmed by a phase marker. Although the existence of advanced and delayed aMT6s rhythms have been reported previously in the blind, these abnormally timed rhythms were not related to the sleep-wake cycle.[8,10]

Our findings show that circadian disorders in the blind manifest either as a permanent advance or delay in sleep timing in AE subjects or temporary advances and delays in sleep onset, sleep offset, and napping patterns in response to the free-running clock. Notably, this relationship exists despite the masking effect of external social demands. These results collectively suggest that the endogenous pressure to sleep has a significant influence in blind subjects with circadian rhythms disorders and may, therefore, presumably apply to all individuals. The importance of cir-

cadian control of normal sleep has implications in other circadian rhythms disorders (e.g., shift-workers) whose performance and accident rates have been shown to be linked to endogenous circadian rhythms of sleep and alertness.[33,34]

The changes in sleep with phase, observed in freerunning subjects in these field studies, are in agreement with those found in forced desychrony laboratory experiments. In blind[22] and sighted subjects,[5] the Harvard group have shown that total sleep time is maximal when the midpoint of sleep is between 270-45° relative to core body temperature (CBT) minimum (0°) and minimal when the midpoint was at 225°. Although the analysis methods, subjects, and conditions differ, our results in the field correspond well with these laboratory experiments. Field studies of blind subjects, in particular those individuals with no light perception (NPL), offer some advantages when measuring melatonin as a phase marker of the clock and may compliment forced desychrony studies. The absence of light effects eliminates the problem of masking due to melatonin suppression by light, or direct entrainment by light, and also avoids possible confounding influences of any photic and non-photic zeitgeber interactions. However, until it is proven that non-photic zeitgebers do not influence the melatonin rhythm, we cannot be certain that assessment of melatonin rhythms in the blind reflects the true endogenous phase. Different individual responses to non-photic zeitgebers (either via masking or entrainment) may account for the wide variations in tau reported in the blind in the field[8,10,12] in comparison to sighted subjects under laboratory conditions.[35,36]

Another reason why such large differences in tau may exist between individuals may be a difference in the subject's ability to consciously override their endogenous control of behavior. If this is the case, it is intriguing why some individuals appear to be more successful than others. The variation both between and within individuals may be due to the tightness of "coupling" between behavioral and strongly endogenous rhythms and may manifest as different degrees of "relative co-ordination" where two rhythms with different periodicities and/or amplitudes run in and out of synchrony with each other.[37]

In summary, this study shows that most subjects with abnormal aMT6s rhythms have a circadian rhythm sleep-wake disorder (ASPS, DSPS, or non-24h sleep-wake syndrome). It is unlikely that a disturbed circadian clock can account for the sleep disorders reported by subjects with normally entrained aMT6s rhythms. In order to identify circadian sleep disorders, long-term assessment is required, in conjunction with a phase marker (such as aMT6s), which will allows the distinction between circadian and non-circadian type sleep disorders. The study also highlights the potential use of blind subjects to investigate the circadian system especially as the observed phase relationships between behavior and circadian phase are consistent with the findings using complex desychrony studies in sighted subjects. These results should also prompt the assessment of sleep and aMT6s rhythms in the blind, particularly those without conscious light perception complaining of sleep disorders, to ensure that inappropriate sleeping medication is avoided.

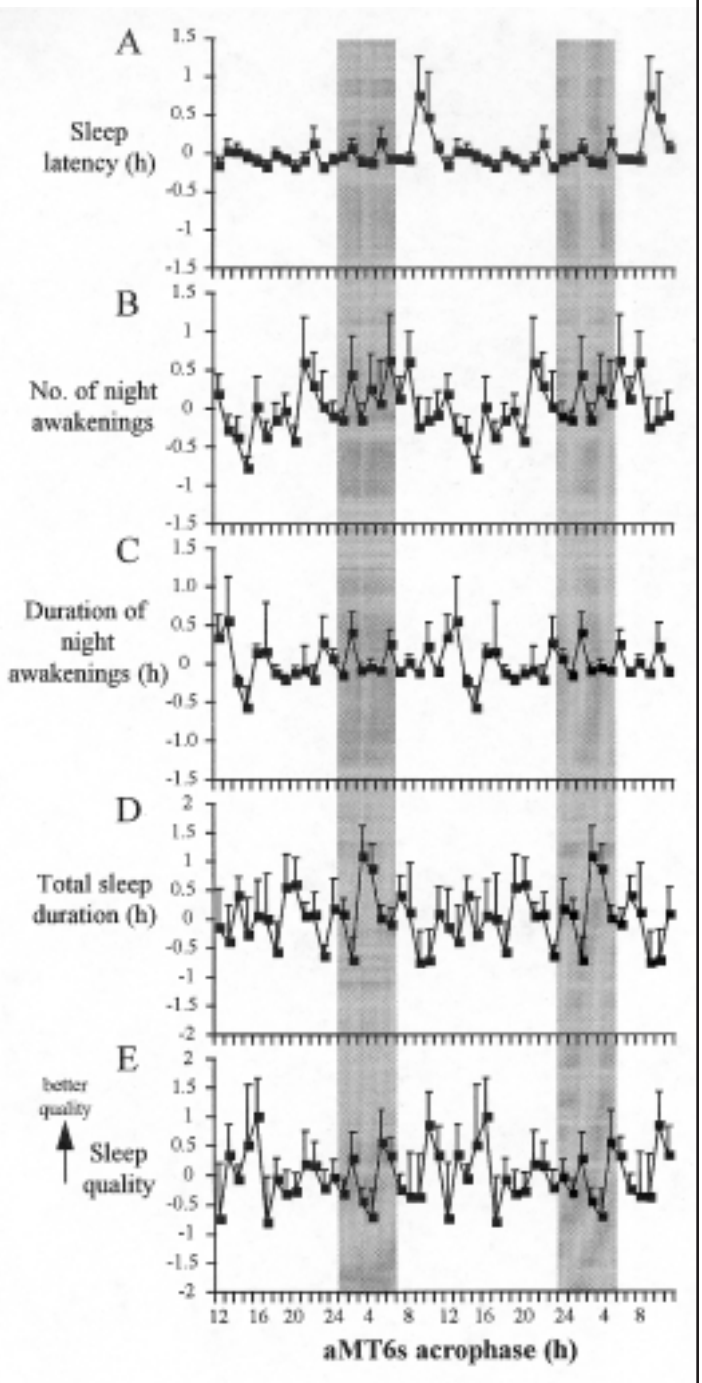

Figure 6. —Relationship between aMT6s phase and sleep in free-running subjects.

The figure shows the mean (± sem) sleep parameters for six subjects (with respect to each subjects' own mean) double-plotted against hourly aMT6s acrophase times. The grey areas represent the mean (±2 SD) aMT6s acrophase time for normally entrained subjects (n=80, English and Arendt, unpublished results). None of the parameters shown changed significantly with respect to aMT6s phase (p>0.05, one-way ANOVA).

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